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Pre-exposure Prophylaxis (PrEP) Scoping and Policy Options Review

EXECUTIVE SUMMARY

HIV Ireland

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Executive Summary

This policy options review and evidence-scoping of Pre-Exposure Prophylaxis (PrEP) for HIV prevention has been commissioned by HIV Ireland Ltd (HIVI) and the Gay Health Network (GHN). The primary aim of this paper is to provide evidence-based guidance on PrEP efficacy, while establishing the views of key populations affected by HIV, and stakeholders directly and indirectly involved in the provision of HIV services throughout Ireland.

This study relies significantly on existing evidence for PrEP particularly reviews conducted by the World Health Organisation (WHO), the National Institutes for Health and Care Excellence (NICE), the National Health Service (Wales), the United States Centre for Disease Control and Prevention (CDC), and the British HIV Association (BHIVA) to reach conclusions about policy options for PrEP in Ireland.

PrEP is a biomedical HIV prevention strategy meaning that it uses antiretroviral drugs to protect HIV-negative people from HIV infection. In August 2016, the European Commission granted marketing authorisation for once-daily Truvada® (emtricitabine 200 mg/tenofovir disoproxil 245 mg; FTC/TDF) in combination with safer-sex practices to reduce the risk of sexually acquired HIV-1 infection among uninfected adults at high risk, which means that once-daily Truvada® is licensed for PrEP in Ireland.

The Evidence-base for PrEP Efficacy

The World Health Organisation's (WHO) Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Recommendations for a public health approach - Second edition (2016) recommends that oral PrEP should be offered as an additional prevention choice for people at substantial risk of HIV. WHO's systematic review and meta-analysis of PrEP trials demonstrated that PrEP is effective in reducing the risk of acquiring HIV infection. It was found that the level of protection did not differ by age, sex, regimen (TDF versus FTC + TDF) or mode of acquiring HIV (rectal, penile or vaginal exposure) but detectable drug levels in the blood are strongly correlated with the prophylactic effect, emphasising the importance of adherence to PrEP.

The sources upon which this study relies - WHO; European Centre for Disease Prevention and Control (ECDC); the European AIDS Clinical Society; British HIV Association (BHIVA); the National Institute for Health and Care Excellence (NICE); the United States Centre for Disease Control (CDC); the Scottish HIV Pre-Exposure Prophylaxis Short Life Working Group and the National Health Service (NHS) Wales - conclude that the quality of the evidence base for PrEP efficacy is robust.[1]. Trials with potentially transferable findings include:

1. WHO, *Consolidated Guidelines,* 2016; Nandwani R and Valiotis G, on behalf of the Scottish HIV Pre-Exposure Prophylaxis Short Life Working Group. *PrEP in Scotland.* Scottish Health Protection Network (SHPN) October 2016; NICE, Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil), 2016; BHIVA-BASHH Position Statement on PrEP in the UK: Update 2016; Center for Disease Control, US Public Health Service, Pre-exposure Prophylaxis for the Prevention of HIV Infection in the United States, 2014; ECDC GUIDANCE HIV and STI prevention among men who have sex with men, 2015; Jones, A., Couzins, Z., Preparing for PrEP? – A Review of the Current Evidence for Pre-exposure Prophylaxis (PrEP) to prevent HIV infection in Wales, NHS Wales, 2017; European AIDS Clinical Society.

1. The iPrEx study was a double-blind RCT evaluating once-daily Truvada® or placebo in 2,499 HIV-negative men or transgender women who have sex with men with evidence of high-risk behaviour for HIV infection. Once daily Truvada® reduced the relative risk of acquiring HIV infection by 44% compared with placebo;
2. The Partners PrEP study was a double-blind RCT evaluating once-daily single agent tenofovir disoproxil or Truvada® or placebo in 4,747 HIV-negative individuals in a heterosexual partnership with a person already infected with HIV in Kenya and Uganda. Once-daily Truvada® reduced the relative risk of acquiring HIV infection by 75% compared with placebo;
3. The PROUD study was an open-label trial of once-daily Truvada® in 544 HIV-negative men or transgender women who have sex with men in England. Participants were randomised to start PrEP with Truvada immediately on study entry or after a deferral period. Once-daily Truvada reduced the relative risk of acquiring HIV infection by 86% compared with no prophylaxis;
4. The IPERGAY study was a double-blind RCT evaluating Truvada® or placebo taken 'on demand' before and after sexual activity in 414 high-risk MSM in France and Canada. Participants took a median of 15 tablets per month and reduced the relative risk of acquiring HIV infection by 86% compared with placebo.

The Bangkok Tenofovir Study is the only large-scale study conducted with people who inject drugs (PWID). Over 2, 400 PWID were enrolled and with optimal adherence a 70% reduction in HIV incidence was reported but in general, this RCT reported a 48.9% reduction in HIV using once daily Tenofovir disoproxil fumarate (TDF) without Emtricitabine (FTC) among PWID. The policy context for this study differs significantly from the Irish context and as such, the high levels of adherence may not be relied upon.

While these population trials provide generally unbiased indicators of the effect of PrEP on HIV incidence rates, they do not provide insight into the effectiveness of PrEP in real-world clinical care settings. Implementation research is needed in diverse settings not least in terms of supporting adherence and the capacity of already over-stretched health systems to respond effectively to increased demand. It is also largely unknown how PrEP may affect behavioural and social outcomes in the medium to long term. The RCTs described here noted few changes in terms of sexual behaviours but trials provide a high level of psycho-social support that may not be replicated in real-world settings.

The cost-effectiveness of PrEP is frequently cited as a key barrier to PrEP implementation and Gilead Science's application for a Supplementary Protection Certificate for once-daily Truvada® is a significant threat to taking PrEP to scale in Europe. Cost effectiveness analysis appears to be particularly sensitive to key variables such as HIV incidence, levels of adherence, demand for PrEP, risk behaviours, the cost of drugs and other clinical interventions required to support PrEP programmes: as such cost-

effectiveness studies conducted in other jurisdictions are of limited value to the Irish context. While France is the only country in Europe currently providing PrEP through the public health service, a number of countries are implementing or planning to implement PrEP demonstration projects.

National and International PrEP Policy Context

The national and international policy architecture for PrEP is well established. The transnational dimensions of health are facilitated through governance structures which foregrounds global and local connectivity. Ireland emphasises an all-of-government approach with policy coherence prioritised between the Health Service Executive and Irish Aid's global health and HIV partnership portfolio, illustrating the extent to which health policy is increasingly perceived to be international in scope. PrEP is already governed – directly and indirectly - by international policy instruments that have been ratified by Ireland. The most recent of these, the 2016 United Nations Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030, was adopted at the United Nations General Assembly High-Level Meeting on AIDS in June 2016, and includes explicit commitment to the adoption of evidence-based prevention measures including PrEP. Furthermore, UNAIDS is a key partner in Ireland's Global Health and HIV Portfolio to which overseas development assistance commits €2.7 million per annum.[2] To fast track actions to achieve 2020 targets, the new Action plan for the health sector response to HIV in the WHO European Region 2017-2022 emphasises the need for member states to optimise prevention efforts through the prioritisation of evidence-based HIV prevention urging a particular focus on key populations, `with inclusion of novel approaches such as pre-exposure prophylaxis (PrEP) for populations at substantial risk of HIV acquisition'[3] Also of continuing relevance, the Dublin Declaration, 2004 commits member states in Europe and Central Asia to act collectively in tackling the HIV/AIDS epidemic, setting out a number of actions to accelerate the achievement of this commitment. The most recent special report under the Dublin Declaration 2016 particularly emphasised the need to reduce HIV infections in Europe using a range of prevention interventions including PrEP. Finally, at national level, policy provision for PrEP is contained in the National Sexual Health Strategy 2015-2020 which urges the implementation of guidelines for the appropriate use of antiretroviral therapy in HIV prevention.

2. 2015 budget allocation
3. WHO Europe, *Action plan for the health sector response to HIV in the WHO European Region,* 2017-2022, Geneva

An Overview of Findings and Recommendations

Following careful consideration of the evidence-base for PrEP, this study conducted a wide range of key informant interviews with stakeholders in Ireland including civil society activists, policy makers, health care providers and researchers, pharmaco-economists, international development specialists, with two focus group discussions (FGD) undertaken with MSM and people living with HIV. Given the paucity of data available on the potential or rationale for introducing PrEP in Ireland, opportunities to verify or triangulate information were limited. In order to present a clearer picture of the Irish-specific landscape, data from this research was collated with pre-existing Irish-specific grey literature and academic sources, with outlier issues and/or data corresponding to ToR requirements not previously considered. The primary findings and recommendations resulting from this process are presented here in summary:

1. Policy options for the introduction of PrEP into Ireland as indicated by the evidence base governing PrEP efficacy; the global, regional and national policy context; the high risk profile of most at-risk populations; the epidemiology of HIV in Ireland, which reflects broader European trends; the views of health care providers and key stakeholders working directly and indirectly in HIV, and the views of potential end users, point to one option: This review identified overwhelming support for the introduction of PrEP for populations at substantial risk of HIV in Ireland as part of a comprehensive package of HIV prevention interventions.
2. An albeit limited level of self-administered PrEP use among MSM appears evident in Ireland, but which nonetheless requires urgent intervention by statutory services in collaboration with civil society who may be well placed to provide immediate information, education and guidance for PrEP users. It is recommended as a first step, that the safety concerns posed by the online purchase and self-administration of PrEP in Ireland must immediately prompt the funding and establishment, within existing specialist sexual health clinics, of information, advice and clinical monitoring services until such time as PrEP is made available through the HSE.
3. The evidence base, while currently dependent on RCTs and a small number of implementation studies, which are increasing in number, clearly demonstrates PrEP efficacy particularly for MSM and transsexual women. Notwithstanding the absence of context-transferable evidence for key populations other than MSM and trans women, the World Health Organisation recommends that oral PrEP should be offered as an additional prevention choice for all people at substantial risk of HIV as part of a combination of prevention approaches, which is widely supported by contributors to this review, while recognising that the primary beneficiaries of potential PrEP introduction are likely to be MSM in practice.

4. PrEP in practice is marked by a number of unknowns with regard to adherence levels, the potential for risk compensation, and of particular concern to health care providers interviewed in this study, the capacity of an already over-stretched sexual health service to absorb a cohort of HIV-negative clients. Implementation research is needed in diverse settings not least in terms of supporting adherence and the capacity of already over-stretched health systems to respond effectively to increased demand. It is also largely unknown how PrEP may affect behavioural and social outcomes in the medium to long term. The vast majority of contributors to this review favoured an implementation or demonstration study as a first step not least because the budget impact may be contained, any unintended consequences more easily offset and issues resolved before PrEP is taken to scale. Concerns about the cost of PrEP were frequently cited as a perceived barrier to PrEP implementation: this is a Europe-wide concern, not just an Irish one. Clinical interventions are not cost-neutral and the actual cost of once-daily Truvada® for PrEP is likely to impact significantly on the budget for HIV and sexual health. An implementation trial would facilitate cost-containment until such time as generic substitutions are licensed for PrEP in Europe. As a first step, it is recommended that GHN and HIVI support the introduction of an implementation study, which may be more easily and speedily sanctioned, until such time as PrEP may be taken to scale.
5. The cost-effectiveness of PrEP appears to be particularly sensitive to key variables such as HIV incidence, levels of adherence, willingness to use PrEP, risk behaviours, the cost of drugs and other clinical interventions required to support PrEP programmes: as such cost-effectiveness studies conducted in other jurisdictions are of limited value to the Irish context. The potential cost of PrEP is perceived to be a barrier to implementation in Ireland. In the medium to long term, there is a role for advocacy in challenging the HSE to explore the cost-saving potential of generic substitution of ARVs which have been found to be acceptable to patients and HIV health care providers, while Return on Investment analysis should be considered in conjunction with budget impact and cost effectiveness analysis which may prove to be a more propitious cost benefit benchmark for PrEP implementation in Ireland.
6. Coupled with concerns about the cost of PrEP and the capacity of the health system to respond to the clinical requirements of PrEP introduction, some participants raised questions as to whether PrEP should be made available to non-Irish citizens. This is problematic in public health terms given that at least 55% of HIV cases diagnosed in Ireland originate from other countries. [4] Additionally, 35% (n=94) of people testing HIV+ in Ireland in 2015 were born in sub-Saharan Africa, and over half (53%) of female cases were born in sub-Saharan Africa. To fail to provide PrEP to non-Irish citizens

4. Geographic origin is unknown in 15% of cases (HPSC, 2015, p.12-13)

may potentially offset any HIV prevention gains and institute non-coherence between Ireland's national and international health policy commitments. It is recommended that policy advocacy must ensure that PrEP implementation does not operate eligibility on the basis of citizenship but works to ensure inclusiveness on public health terms and in the interests of a 'whole-of-government' approach.

7. Europe's Action plan for the health sector response to HIV in the WHO European Region, 2017-2022 urges member states to "collect and analyse timely and high-quality epidemiological data to understand how, where and among whom new HIV infections are occurring, develop HIV estimates, monitor risk behaviours and estimate the size of key populations in need of services."[5] Ireland's failure to prioritise and invest in the collection of epidemiological data is a significant risk to cost-effectiveness, budget impact and service planning estimates for PrEP and other interventions, while also precluding full engagement and reporting against high profile international commitments, including 90-90-90 targets. A number of participants in this study raised the need for increased behavioural surveillance investment to help identify and better off-set risk by early intervention. There is a role for civil society to champion improved surveillance systems in Ireland so that new technologies (like PrEP) are supported by robust epidemiological data and evidence.
8. Civil society advocacy is central to the realisation of particularly contested policy issues, and plays a key role in holding government and statutory service providers to account. While advocates for PrEP implementation are an important part of the process, Ireland's relatively conservative political culture points to a generally cautious approach to policy change for sexual health. Views were divided on the best approach to policy advocacy for PrEP but it is suggested that advocacy platforms for PrEP might be best served by campaigns targeting key policy makers, while mobilising political champions to engage stakeholders in dialogue to help remove some of the barriers to PrEP implementation. Civil society representatives need to be prepared for media interest in PrEP with a factually based public health narrative that is devoid of emotive arguments and rests on sound science.
9. Finally, it is a flawed rationale that renders the statutory services ever the subject of complaint when private interests like Gilead Science Inc are the primary reason why PrEP affordability and cost effectiveness is questionable. Gilead's application for an SPC for Truvada® is the single most significant threat to taking PrEP to scale in Europe not just in Ireland and this issue requires strong civil society engagement.

5. WHO Europe, 2016, p.8

Conclusion

A combination of the evidence for PrEP efficacy coupled with the risk profile of key populations in Ireland, increasing incidence of HIV reflecting broader European trends, PrEP's policy coherence with Ireland's international policy position, and a high level of support for PrEP implementation among key stakeholders and potential end-users, points to the need for immediate steps to be taken to make PrEP available to key populations at substantial risk of HIV acquisition as part of a comprehensive package of HIV prevention measures. At an absolute minimum, the failure to provide HIV testing and clinical monitoring to MSM who are self-purchasing and administering PrEP is a risk to the individual and broader public health. While multidrug resistance levels are generally low, the risks are increased if people with an undiagnosed HIV infection are acquiring PrEP online. The global, regional and national policy context actively advocates PrEP implementation and the requirements to prioritise HIV prevention in member states of the European Union where sexually acquired HIV incidence rates are raising exponentially must render PrEP a policy priority in Ireland.

Limitations of the Review

This policy options review and evidence-scoping of PrEP for HIV prevention was time-limited with parameters and scope clearly determined by the Terms of Reference. It relies significantly on existing evidence for PrEP particularly reviews conducted by a range of multilateral, national and international institutes for health to reach conclusions about policy options for PrEP in Ireland. Much of the information synthesised and presented in this paper was provided by those with direct or indirect involvement in HIV and sexual health in Ireland and is consequently not free of bias. The reviewer has endeavoured to critique key informant responses where possible but the paucity of grey or academic sources relating to PrEP in Ireland limited the robustness of this exercise. The limitations imposed by time and the breadth of ToR requirements; the paucity of the Irish-specific evidence base; the poor participation of stakeholders from outside Dublin and stakeholder bias necessitates some generalised findings. As such, the findings and conclusions presented herein must be interpreted with caution.

HIV Ireland is a registered charity operating at local, National and European level. The principal aim of the organisation is too improve, through a range of support services, conditions for people living with HIV and AIDS and/or Hepatitis, their families and their caregivers while further promoting sexual health in the general population.

Our mission and vision is to contribute towards a significant reduction in the incidence and prevalence of HIV in Ireland and towards the realisation of an AIDS-free generation by advocating for individuals living with HIV, preventing new HIV infections and combating HIV-related stigma and discrimination.

Since 1987 HIV Ireland has been pioneering services in sexual health education and promotion, and has consistently engaged in lobbying and campaigning in the promotion of human rights. Our approach broadly reflects a harm minimisation model which emphasises practical rather than idealised goals. In relation to practical service provision we currently operate under two headings:

Community Support

- Counselling
- 1-1 Support
- Advocacy
- Community Outreach Work
- HIV & STI Community Testing
- Capacity Building with People Living with HIV

Prevention, Education & Training

- One day workshops on HIV, STI's and Sexual Health
- Sexual Health Training for Trainers Programme (Let's Talk About... Safer Sex)
- Free Condom Service (Just Carry One Campaign)
- Social Media work and campaigning
- Network Involvement

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