Health Intelligence

Shift HEALTH

PrEParing for Success in Pre-Exposure Prophylaxis

PrEP has tremendous potential across a range of infectious diseases, and ***innovators need to be ready.***

Pre-Exposure Prophylaxis (PrEP), which has become a mainstay of HIV prevention, is emerging as a valuable approach to protect at-risk individuals against infectious diseases beyond HIV. To capture opportunities in this expanding area, innovators will need to account for unique clinical, commercial and access considerations. **Our aim is to present five considerations at the product or portfolio-level that we believe are key to positioning PrEP programs for success.**

- ***Programs should focus initially on at-risk populations*** that may not benefit from existing prevention tools (e.g. vaccines), including immunocompromised groups, individuals with multiple co-morbidities, healthcare workers and potentially others in frequent contact with those at-risk.
- ***PrEP's value proposition should emphasize convenience, cost-effectiveness and ease of use,*** with a focus on durability, complementarity to vaccination and seamless integration at the frontlines of delivery.
- ***Significant investment will be needed to prepare markets***, with a focus on building awareness of the limitations of vaccines in target populations and the distinguishing features of PrEP from other prevention and treatment approaches.
- *A **PrEP portfolio should be positioned to support combination or co-administration of individual products*** to maximize convenience for patients and health systems and deliver as much protection as is valuable in a single PrEP visit.
- ***Stockpiling should be factored into the opportunity*** by emphasizing attributes that increase government's confidence in PrEP's utility (e.g. breadth of coverage across pathogen types), and exploring inventory and surge capacity models that make the most compelling case to systems.

These considerations will underpin winning playbooks for PrEP programs and position them to fulfill their health and commercial potential.

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CONTEXT

Despite the irrefutable benefit of vaccines and other prevention measures, the burden of both acute and chronic infectious diseases (IDs) remains high. In 2019, lower respiratory tract infections alone were the fourth leading cause of deaths globally (~5%)[1]. This burden is amplified in at-risk populations (e.g. immunocompromised), as exemplified by the tragedy of the COVID-19 pandemic and the devastating impact of outbreaks of seasonal pathogens such as influenza and RSV (see **Fig. 1**).[2,3,4] Clearly, our prevention tools are not perfect as they fail to address the needs of immunocompromised and immunosenescent individuals who are unable to respond fully to vaccines.

To better protect at-risk populations from ID threats, we need to expand the prevention tool chest, including innovations that offer passive protection before exposure to key pathogens.

PRE-EXPOSURE PROPHYLAXIS

Pre-Exposure Prophylaxis (PrEP) refers to the use of medications that prevent the acquisition and transmission of IDs. PrEP is distinguished from vaccines because it offers 'passive' protection that does not require an individual to mount an immune response. The approach was demonstrated in HIV, where antiretrovirals are used by non-infected individuals at high risk of exposure. While effective, HIV PrEP adoption has faced challenges, some of which may translate to other disease areas (see **Fig 2**).[5] Indeed, these access considerations should be considered as innovators advance PrEP programs targeting pathogens beyond HIV (see **Fig. 3** for an *abbreviated* pipeline view).

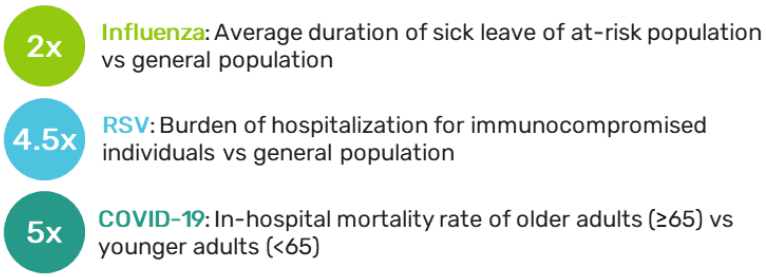

Fig. 1: Amplified Burden of ID in At-Risk Populations

Given potential access challenges and relative nascency of the field, PrEP is associated with unique considerations that warrant the attention of innovators if they are to deliver on the expected health benefits and commercial returns.

STRATEGIC CONSIDERATIONS FOR PREP DEVELOPMENT

Here, we present five considerations that are key to positioning PrEP programs/portfolios for success.

Initial focus should be placed on at-risk populations.

With vaccines an enduring mainstay of preventive care, PrEP should be positioned as a complementary tool designed to address unmet needs for populations at-risk of progressing to severe disease. These populations include: i) immunocompromised populations who cannot fully respond to vaccines (e.g. older adults, individuals with autoimmune disease); ii) individuals with comorbidities requiring an additional layer of protection (e.g. cancer patients); and, iii) healthcare workers frequently exposed to harmful pathogens. It may also be valuable to address populations that frequently come into contact with high-risk groups; here, demonstrating that PrEP can reduce transmission may be worthwhile.

While potentially challenging to make the case for PrEP targeting a more 'general' population, there may be an opportunity where PrEP demonstrates significant advantages over vaccines. In this case, the degree of direct competition would expand to vaccine players who are aiming to close gaps with new technologies like mRNA (e.g. greater influenza vaccine efficacy).[6,7] While it remains an uncertainty[8], should these new approaches in fact lead to better responses, the value proposition

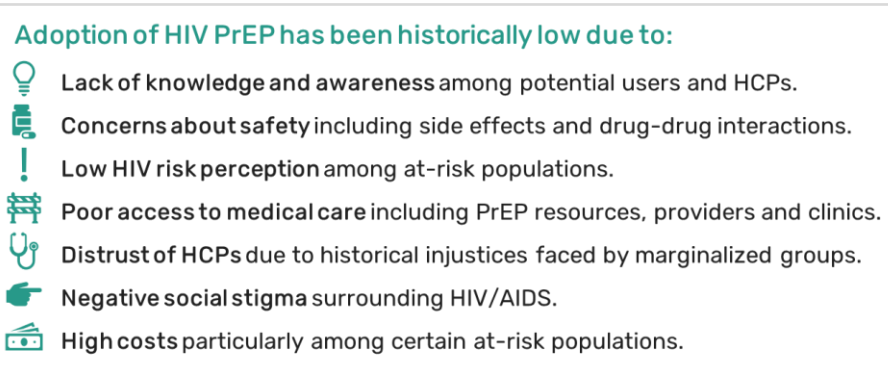

Fig. 2: HIV PrEP Adoption Challenges

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Company	Asset	Disease	Dosing	Phase 1	Phase 2	Phase 3	Submitted	Approved	Withdrawn
janssen CIDARA	CD388	Influenza	Potential for a single dose to last a flu season		Phase 2a				
VIR	VIR-2482	Influenza A	Potential for a single dose to last a flu season		Phase 2				
AstraZeneca sanofi	Nirsevimab	RSV	Single dose				BLA submitted		
GILEAD	Lenacapavir	HIV-1	Twice yearly					FDA approved	
ViiV Healthcare	Cabotegravir /rilpivirine	HIV-1	Every 2 months					FDA approved	
AstraZeneca	Tixagevimab /cilgavimab	COVID-19	Every 6 months						EUA withdrawn

Fig. 3: Abbreviated PrEP Pipeline (non-exhaustive)

for PrEP becomes more complex. With that, there is a portion of the general population hesitant to use any vaccine and PrEP technologies may appeal to some in certain circumstances.

PrEP's value proposition should focus on convenience, cost-effectiveness and ease of use.

An ideal target product profile for a PrEP asset needs to consider *three central principles*.

First, convenient dosing will be critical for PrEP. In contrast to post-exposure prophylaxis, where daily dosing may be acceptable given the short duration, PrEP could be required for months (e.g. seasonal disease) or years (e.g. for HIV). Frequent dosing will therefore pose a challenge, potentially resulting in lower compliance, lower effectiveness[9] and even resistance.[10] Where relevant, it may be attractive to mirror a familiar vaccine regimen by launching with a long-acting (LA) formulation. For example, nirsevimab[11] is an engineered antibody that extends its half-life for a whole season while cabotegravir/rilpivirine's novel formulations allow for injections every two months.[12] Given that individuals cannot pause dosing with these LA formulations (as one could with daily pills), particularly those with co-morbidities who may undergo routine treatments, careful consideration for unique drug-drug interactions may be required.[13]

Second, cost-effectiveness should also be considered. For developers to receive favorable reimbursement coverage, they will have to articulate value in terms of PrEP's complementarity to vaccines and prove that the net public health return is greater than the sum of its parts. This argument may have implications on trial design and the need to show more than incremental benefit. Indeed, for HIV PrEP, the "overwhelming" benefit is now translating into greater reimbursement coverage, including for labs tests and clinical visits.[14,15] A deep appreciation for not only the health system burden but also the societal and economic burden (e.g. work absenteeism) of infection-related illness will be critical in establishing a compelling case. Moreover, these data will help to achieve the broadest recommendation possible from oversight groups like ACIP, who have recently reviewed data on nirsevimab and whose guidance is largely followed by systems and payers.[16]

Third, ease of use and integration into the clinical decision-making process at the frontline of care will also be crucial. As immunization schedules become more intricate and combination vaccines come to market, the complexity at the frontlines will increase. PrEP will therefore have to integrate seamlessly into the decision-making process, potentially supported by digital health solutions that help providers recommend PrEP use.

Significant investment will be needed to prepare markets.

Even in the case of HIV, a disease with high awareness among those at risk, adoption of PrEP is relatively low. It is therefore expected that, like most emerging fields, PrEP users, prescribers and payers will require significant education to drive adoption. Awareness building should emphasize the limitations of vaccinations for target groups and the distinguishing elements of PrEP compared to treatment, which are often associated with the perception that they are ineffective and may require a diagnostic to justify their use. Potential policy barriers should be addressed, with proposed, evidence-based solutions that will benefit stakeholders and address access hurdles. For example, in some disease areas, it may be ideal if pharmacists were empowered to prescribe and

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deliver PrEP (similar to vaccines) in order to alleviate system burden and provide convenience to target groups, which themselves will require significant education to seek out PrEP in this model.

A PrEP portfolio should be positioned for future co-administration or combination of individual assets.

With the need for significant market development, the ability to advance solutions that could be combined at the point of delivery is likely to benefit from efficiencies and see greater adoption. Considerations at the portfolio level should therefore factor in the overlap in target populations and disease areas (e.g. respiratory diseases like influenza, RSV, COVID-19 or sexually-transmitted diseases like HIV, HTLV, Hepatitis B). A case to focus on generally less harmful infectious diseases (e.g. HSV, EBV, CMV and adenoviruses) may be heightened given the focus on more at-risk populations and the disproportionate burden among these groups.[17] PrEP combinations can also consider a similar model to vaccine combinations.[18] This approach will require innovators to demonstrate the benefit of combos vs. individual assets while factoring the implementation realities at the frontlines in terms of stocking, logistics and supply. PrEP portfolios built on the same platform technologies are likely to simplify this approach overall.

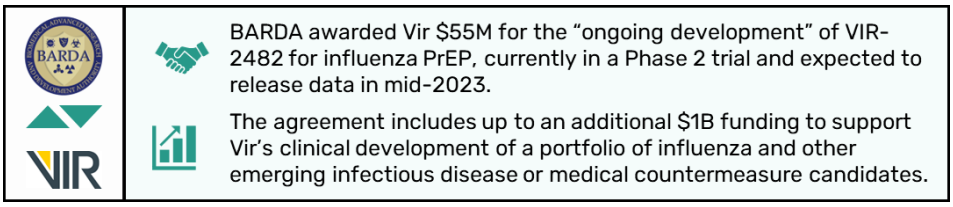

Fig. 4: BARDA and Vir partnership focused on advancing flu and other PrEP assets.

Stockpiling should be factored into the commercial opportunity.

With a mechanism of action that can provide rapid protection and the potential ability to target conserved regions of pathogens that are not necessarily immunogenic, PrEP assets can also play an important role in pandemic preparedness. To make the case to governments and systems seeking to bolster their stockpiles of preventive solutions, developers should consider product attributes such as storage conditions, shelf-life and breadth of protection across pathogen subtypes that increase confidence in their use. Unique business models (e.g. insurance-based models, surge capacity models) may also help to make the case by facilitating inventory management. Indeed, some organizations are already partnering with systems to advance PrEP (Fig. 4).[19] With pandemic preparedness heightened in the minds of government, the opportunity for companies to act as partners to address this urgent need is likely to grow.

CONCLUSION

Many at-risk populations will not be able to reap the full benefits of emerging vaccine technologies, creating an opportunity for more passive protection approaches like PrEP. Developers seeking to deploy PrEP assets will have to break through the noise, tailor their assets to populations in greatest need, offer durable solutions that drive adoption and communicate clear messages to stakeholders in order differentiate PrEP solutions in the marketplace. PrEP portfolios can piggy-back on and complement the evolution of vaccine combinations but must similarly focus on the points of synergy across populations and pathogens in order to maximize convenience. Finally, the ability to heighten population preparedness against known and unknown threats through stockpiling should be factored into the opportunity to advance these highly needed programs.

There are reasons to believe that PrEP can become a mainstay prevention tool. With portfolio and product strategies that account for PrEP's considerations head-on, organizations can position themselves as leaders in this effort.

REFERENCES

[1] WHO. 9 Dec 2020.
[2] *Influenza, Resp Viruses*; 2022;
[3] *Vaccine*; 2022.
[4] *Phys. Int*; 2022.
[5] *Adv. Ther*; 2020.
[6] CDC; 2022.
[7] *PNAS;* 2022.
[8] Reuters; 2023
[9] *J Acq. Imm. Defic Synd*; 2016.
[10] *AIDS*; 2009.
[11] *N Engl J Med*; 2022.
[12] Healio; 6 Feb 2022.
[13] *Inf. in Med*; 2022.
[14] CNBC; 11 Jun 2019.
[15] STAT News; 20 Jan 2022.
[16] ACIP; 20 Oct 2022.
[17] *Breathe*; 2022.
[18] FiercePharma; 23 Jan 2023.
[19] Vir: 4 Oct 2022.

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