

From presumptive exclusion towards fair inclusion: perspectives on the involvement of women living with HIV in clinical trials, including stakeholders' views

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Introduction

This article explores the meaningful involvement of women living with HIV in clinical trials from multiple perspectives. Clinical trials are research studies performed among people that are aimed at evaluating a medical, surgical, or behavioural intervention. Women have long been involved in trials as recipients of trial medication or placebos and as women answering questions created by others for others' research. Until recently, this is what 'trial participation' has entailed for women. Various articles have rightly raised concerns about the relative paucity of women's participation in trials, compared to men, highlighting that the problem seems to be particularly bad in the context of HIV.¹

However, times have moved on, and for some time, women living with HIV – supported by some clinicians and other women's rights advocates – have not only been calling for equity in terms of numbers. They have been calling also for something much more inclusive and fundamental: their meaningful involvement throughout the clinical trial process. This article explores what this means in practice from the perspective of a variety of different 'stakeholders', including HIV consultants, women living with HIV, and a gender and health policy analyst. While each section has been written independently, we present them

all here in one article, in order to share a more rounded viewpoint on this topic than is usually reflected in the literature.

Background – the perspective of consultants in sexual health and HIV medicine

Despite making up more than half of the global population of people living with HIV,² women are under-represented³ in HIV treatment,⁴ cure,⁵ and vaccine⁶ clinical trials. This has led to a dearth of scientific knowledge on the efficacy, safety, and tolerability of HIV treatment among women. In this article, we review the impact of this, historic barriers to participation and suggest ways to achieve more equitable recruitment.

A systematic review³ of HIV research trials published in 2016 found that although there had been a significant increase in the participation of women, they had not yet reached parity. Women only represented 19.2% of participants on antiretroviral (ARV) studies, 38.1% in HIV vaccine studies and 11.1% in HIV cure studies. Looking at the regulatory randomised control trials for the recently licenced ARVs bicitegravir, tenofovir alafenamide, dolutegravir, and doravirine, Pepperrell *et al.*⁴ estimated that globally white men were over-recruited by around 44% compared with their global burden of disease, while

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black women were under-recruited by around 35%. They also found that despite most of the global burden of HIV being in low and low-middle-income countries, most of the trials were carried out in high and high-middle-income countries. A systematic review⁵ of HIV cure research published in 2015 found that women, as well as older people and those of non-white ethnicities were profoundly under-represented.

This pattern of under-recruitment is not only seen in HIV, but in many disease areas including cardiovascular disease,⁷ cancer,⁸ and mental health conditions.⁹ Sex and gender differences¹⁰ in the prevalence, incidence,¹¹ symptomatology, and progression¹² of a range of diseases have been described, as have differences in responses to treatment. These differences in treatment responses are likely to be attributable to differences in how the body deals with a drug (pharmacokinetics) and the effect of the drug on the body (pharmacodynamics). This may affect the efficacy and tolerability of the drug.¹³ Importantly, sex¹⁴ and gender¹⁵ inequalities¹⁶ in social and economic power also have a large impact on health outcomes, affecting health-seeking behaviour, access to, and utilisation of healthcare services.

In HIV, sex and gender differences have also been described as making women vulnerable to acquisition, access to services, rate of disease progression, and response to ARV treatment. Adverse events and tolerability to ARV medications have been shown to vary by sex and gender, which again is likely due to differences in pharmacokinetics and pharmacodynamics including body surface, hepatic function, drug metabolism, absorption, and clearance.¹⁷ For example, cisgender women are at increased risk for rash, lactic acidosis, pancreatitis, and lipodystrophy.¹⁸ This may in part explain sex and gender differences¹⁹ in treatment adherence²⁰ and viral suppression. It is therefore vital that sufficient information is known about sex and gender differences and similarities, so that treatment is optimal and evidence-based for all people living with HIV. Increasing the participation of women in HIV research is also an ethical issue, as women should have equal rights to sufficient scientific knowledge to make an informed decision about a treatment. If this knowledge does not exist, they cannot be fully informed.

A range of barriers²¹ to participating in HIV clinical research²² for women has been described.²³

These include concerns about safety or side-effects, confidentiality, stigma, lack of trust in researcher or research, worries about research methods or requirements, a lack of information, and language barriers. Structural factors such as low socio-economic status and gender inequality mean that women may be less likely to have enough time, money, or available transport to take part in research and may have competing responsibilities such as childcare. Women living with HIV are also more likely to experience partner violence which may impact on their decision-making ability to agree to taking part in research. Researchers may also hold stereotypical beliefs that women and minoritised groups are more difficult to recruit, and this bias²⁴ may in turn make them less likely to approach these groups.

Historically, there has understandably been concern about the potential harmful effects of experimental drugs to the foetus. This means that most trials exclude women who are pregnant or breastfeeding, and if a woman becomes pregnant during a trial, she may be taken off the experimental drug.²⁵ As a consequence, many trials have strict contraception guidelines. These can deter women from taking part in the research. This may particularly affect women who come from cultures which place a high societal value on fertility and childbearing. We discuss these issues in more depth further on.

Some positive steps forward

Despite considerable barriers to research for women, there are many interventions²⁶ which may address these. A survey²⁷ carried out of women living with HIV in Canada in 2014 found that it was important that research personnel were respectful, skilled, flexible, and empathic with good communication skills. They recommended that they try to develop a strong rapport with potential participants facilitated by an empathetic relationship that they acknowledge the sensitive nature of the research topic, provide cash-based financial compensation, and develop recruitment strategies unique to women. In addition, Grewe *et al.*²⁷ recommend addressing eligibility criteria and structural barriers to participation, adapting recruitment strategies, engaging community members early in the research process, and promoting funder policy changes to prioritise recruitment equity. Several studies have shown that a diverse range of women can be recruited to

clinical trials. These include the GRACE (Gender, Race and Clinical Experience) Study, a phase-III ARV trial of which 67% of participants were female.²⁸ This was thought to be due to careful planning and research of the local context of each site, the engagement of community advocates, decreasing exclusion criteria and mandating enrolment quotas for women. However, this had a higher discontinuation rate for women than men, showing more work needs to be done to facilitate retention in care. Trials aimed solely at women have also started to be designed, such as WAVES (Women AntiretroViral Efficacy and Safety Study), a phase-III multicentre study investigating the integrase inhibitor Elvitegravir²⁹ and ARIA, a phase-III multicentre study investigating the fixed-dose abacavir/lamivudine/dolutegravir.³⁰

The exclusion of pregnant and breastfeeding women in trials

Since the Thalidomide crisis in the 1960s, women of reproductive potential have been excluded from clinical research. This continued exclusion of pregnant women from research has resulted in a gap of scientific evidence on how to manage them. This has led to millions of women living with HIV having received ARV drugs with insufficient safety or efficacy data.³¹ There are significant physiological changes to the body in pregnancy which may affect pharmacokinetics and pharmacodynamics of a drug. This may result in a lower exposure of drug in pregnancy risking failure³² of the treatment. Tolerability may also differ for pregnant women. It is therefore important that any differences due to pregnancy are investigated. The lack of inclusion of pregnant and breastfeeding women in clinical trials also means an inequity of access to newer and potentially more effective and tolerable ARV medications.³³

To try and understand efficacy, safety, and teratogenicity in pregnancy, the use of data from animals and surveillance studies has been used, eg, the ARV pregnancy register in the United States. However, these methods have been shown to not always be accurate. For example, there were signals that efavirenz, a widely used ARV may cause neural tube defects. This was seen in retrospective case reports in humans and in monkey foetuses. This led to a recommendation from the World Health Organization in 2005 that Efavirenz

be avoided in women of childbearing potential. This was subsequently reversed in 2012 after several meta-analyses showed no increased risk. However, this meant that many women had been denied access to a safe and efficacious drug for several years, due to concern about teratogenicity.³⁴ Surveillance data can be useful at picking up early signals of possible teratogenicity, but findings may change with time as more data are collected. For example, the Tsepamo surveillance study showed a signal of possible teratogenicity associated with dolutegravir, but this was reduced with data from more women using dolutegravir in pregnancy.

Outside of HIV, the COVID-19 pandemic has shown that pregnant women are less risk-averse than expected, with many asking for access to the new COVID-19 vaccines.³⁵ Pregnancy can also worsen COVID-19 outcomes, so preventing and treating COVID-19 is a priority. However, most COVID-19 treatment trials have excluded pregnant women.³⁶

Weld *et al.*³³ describe how through decades of activism, the paradigm in HIV has shifted from ‘a paternalistic framework of protecting women from research to a perspective of protecting women through research’ and how this is particularly relevant with regards to pregnancy. An example of this comes from Fairlie *et al.*,³⁴ who suggest a step-wise approach to including pregnant women in trials. They recommend that investigational drugs be systematically stratified by pregnancy risk profile from low to high risk, based on guidelines from regulatory bodies. This ‘stratification should determine the progress through preclinical work with animals and non-pregnant women to opportunistic studies among women who become pregnant on a clinical trial or within routine clinical treatment’. They go on to explain that

stratification can include pregnant women in clinical trials, concurrent with Phase II/III trials in non-pregnant adults, and ultimately to postmarketing surveillance for outcomes in pregnant women and their infants. Each step can be enabled by clear criteria from international and local regulatory bodies on progression through study phases, standardized protocols for collecting relevant data, collaborative data sharing, pregnancy outcomes surveillance systems supported by committed funding for these endeavours.

Encouragingly, this year, the FDA (Food and Drugs Agency) in the United States, the EMA (European Medicines Agency), and the MHRA (Medicines and Healthcare products Regulatory Agency) in the United Kingdom jointly published a call for action to address this issue, recognising that some work has been done, but there is still much to do.³⁷

RD adds: As an HIV consultant physician with considerable experience of treating women living with HIV, I can see how gaps in research knowledge caused by the exclusion of women in trials impacts on their clinical care. While clinicians endeavour to give up to date evidence-based advice to help women make informed decisions, when that evidence is missing, this can be very challenging. The evidence shows that there are interventions that work that women living with HIV are willing to take part in clinical research if it is designed in a way that suits them. It is therefore of vital importance that efforts are made to implement these interventions more widely, so that women globally can benefit from the safest, most efficacious, and tolerable treatments available.

Women's inclusion in HIV research – why it matters – the perspective of a Peer Navigator in a busy London clinic

My name is Janine Mcgregor-Read. I am a woman living with HIV for the past 30 years.

I work as a peer navigator for the HIV charity Positively UK and my work is based in the Jonathan Mann Clinic, Homerton Hospital where as part of the social care team I will see or speak with any patient diagnosed with HIV who has an aspect of their diagnosis and health that they are yet to come to terms with or who has difficulties with social issues such as isolation, immigration, financial, housing problems. I have been working in this capacity for 7 years.

The majority of patients I work with are black women, mostly between 25 and 65 years.

My role involves listening to the stories, the lives, and the concerns of these women. I bring my lived experience, information about access to services, initiatives in the community and within the NHS to patients in order to help their journey with HIV.

Through my many years living with HIV, I have taken part in several research studies; however, very few were directly tailored to the needs of women. I am happy to say that I was able to work as a peer researcher for the Prime Study³⁸ (2016–2017). My role in clinic and community made it easy for me to recruit women to the study and the research study lead, clinician Dr Shema Tariq, made sure to involve myself and the two other peer researchers throughout every stage of the study. I learnt how to evaluate data and outcomes and contributed to writing and presentation of the report. It was a rich learning experience for me professionally and personally particularly in being part of the dynamic energy, eagerness, and heartfelt sharing with which the invited women entered into the space to discuss the changes their bodies encountered around ageing, menopause, and HIV.

It was abundantly apparent that women had a need of a dedicated space, lots of questions about their experiences, a need to voice, to be heard by peers and clinicians, and to be recognised as a community whose bodies and experiences matter. The focus groups we organised were outstripped by demand to contribute.

Currently I am now recruiting to the Nourish-UK study.³⁹ This research investigates how parents living with HIV make decisions about feeding their babies. Again, I am happy to say my role allows me to work with the specialist midwife routinely and build strong relationships with mothers-to-be and follow-up after birth. All the mothers I have asked are so happy to contribute to the study. It is research that speaks to the most precious moments and decision-making in their babies' start in life.

From my observation, there is a mass of untapped experience, opinion that these women have navigated. Without research, how will informed choice and standards of care be improved for these mothers and their babies? Women living with HIV want to have the opportunity to own as much of their experience and decision-making as possible regarding their overall health.

We have been in relatively successful partnership with our HIV consultants for decades regarding ARVs and U = U (which means that if we have an undetectable viral load, our HIV is untransmittable),⁴⁰ but that dialogue needs to be enlarged

to include more of the awareness of lived experience, and concerns that affect our health, of which HIV is a part.

We also need to have an increased awareness of women's bodies and how this viewpoint intersects with living with HIV. From my perspective, with an emphasis on social care, there is a mass of experience in women's lives that reflects to me as unmet need, questions that pertain to quality of life. For example, a high proportion of women I see are also prescribed anti-depressants. They are struggling to cope – why – any combination of reasons from stigma, poverty, immigration issues, housing problems, and so on, and it is rare that a person I see only needs to speak about HIV. Therefore, problems are often multiple and cumulative. How does the above affect women's bodies? Their minds, their spirit, their lives, and the families they are so often responsible for. Is there a research question in this? Are we a demographic that matters enough for an investigation into the quality of life issues that can ultimately affect adherence and therefore ability to live well with HIV?

I would posit that until such research is done and investment made in the needs of this demographic, the current mantra of 'HIV being a manageable condition' does not hold up well for many women who, if asked, have much to say about complex and poor health experience and as a consequence may also experience a greatly reduced quality of life.

Trial requirements, contraception stipulations, and their impact on women's participation – from a gender and health policy analysis perspective

Contraceptive requirements as a barrier to women's participation and how to address this

While women of reproductive age are frequently ineligible for participation in clinical trials, even those trials for which women are eligible may have off-putting requirements. One of these is regarding the stipulated use of a 'reliable contraceptive method'. There are often sternly worded sections in patient information about the importance of women who find they are pregnant during the study period, telling the trial doctor immediately and being removed from the trial.

These requirements are standard, and there may be very good reasons for advising women to avoid pregnancy during a trial. However, some authors have raised concerns about whether current patterns of contraceptive requirements disrespect women's autonomy, or unduly impose the risks and burdens of contraceptives on research participants;^{41,42} and unfairly impede access to research carrying the prospect of direct benefit.⁴³ The 'high rates of contraceptive failure' in clinical studies,⁴¹ even where consent and understanding of the reasons for avoiding pregnancy has been assessed as high,⁴⁴ suggest that contraceptive requirements and the way they are framed are problematic for women. The use of the word 'failure' resonates with other language issues pointed out by Salamander Trust and others.^{45,46} It denies women's agency and the possibility that they may have made a decision to stop using contraception and become pregnant. It also denies the fact that the 'failure' may be a result of decisions and actions by their male partners and women's lack of agency in their relationships. Some key areas of concern in terms of women's participation in HIV clinical trials include:

'Reliable' and 'unreliable' contraceptives

Study criteria may divide contraceptives into 'reliable' contraceptives (such as injectable DMPA, implant, oral pills, and IUD) and 'unreliable' contraceptives (such as condoms, lactational amenorrhea, and withdrawal). Some trials promote 'reliable' contraceptives to women who are not using any method or who are using an 'unreliable' method (as in the case of *Abaasa et al.*⁴⁷).

However, the reliability of any method depends on how it is used, and on women being able to access ongoing support and contraceptive services. Injectables need to be renewed on time. Oral pills need to be taken daily, and their effectiveness is compromised when people are sick. For some women, internal or external condoms may be their preferred and usual method – and when used well, they are effective at preventing pregnancy. The issues with the categorisation into 'reliable' and 'unreliable' were demonstrated in a feasibility study for an HIV vaccine efficacy trial:

Seven women got pregnant while using reliable contraceptives in the trial. The four women on injectable DMPA had all delayed an injection by about one month perhaps indicating they were

unaware of the need to renew on time. Three women were using oral pills and adherence issues with use of oral pills have been well-documented. In an actual HIV vaccine efficacy trial, these women would have to be withdrawn from the trial. Encouraging women to receive their contraception injection or take their pills on time through phone calls and/or home visits would improve adherence.⁴⁷

Protection from STIs and HIV for trial participants

When contraceptive eligibility requirements exclude condoms and actively promote other methods, are women also advised and supported to continue using condoms if they want to ensure protection from STIs and HIV for themselves or their sexual partners? A focus on avoiding pregnancy for the requirements of the trial may contribute to women's need for STI and HIV prevention being ignored or deprioritised. If women are using another method for the trial, it may make it more difficult, for those who want to, to insist on condom use with sexual partners.

'Inform us immediately if you get pregnant'

For some women, this may feel extremely intrusive, for others less so. However, researchers would do well to bear in mind the discrimination and violations of sexual and reproductive health and rights (SRHR) that women living with HIV have experienced globally. This includes a history of forced and coerced abortions and sterilisation among women living with HIV⁴⁸ and being judged and abused by health providers when they become pregnant. It also includes the challenges women face regardless of HIV status in being able to access

safe abortion services, particularly where abortion is criminalised. Pregnancy desires are often fluid and changing. For women involved in clinical trials, particularly those lasting some time, the desire to become pregnant can outweigh considerations about safety, and for some becoming pregnant was seen as a mitigating factor to relationship breakdown.⁴⁴ Furthermore, clinical trials should perhaps learn from the issues caused by restricting the use of dolutegravir as an HIV treatment in 'women of childbearing potential' (another reductionist term that denies women their agency and personhood). As women living with HIV campaigning against this restriction pointed out,

Our choices should not be removed from us. Access to DTG CANNOT be solely defined by our potential, or an assumed, biological capacity to have children irrespective of our age, HIV status, profession, drug use status, and our sexual orientation or gender identity. (SOGI)⁴⁹

Similarly, clinical trials should avoid making assumptions about women, their sexual lives, pregnancy desires, use of contraceptives, agency, and intimate decision-making.

One size does not fit all

Study criteria and patient information often make no specific provision for people who are not sexually active, or whose sexual activities do not cause pregnancy (such as same sex relationships or solo sex).

Below are some starting suggestions about how to make trial contraceptive requirements more friendly and women centred.

How to make trial contraceptive requirements more friendly?

From our experience, we suggest the following could help to make contraceptive eligibility requirements more person-centred and women-friendly:

- Be aware that requirements for contraceptive use and pregnancy testing as part of trial eligibility can feel very intrusive for participants. Think carefully about how you phrase these requirements and how to make them as respectful as possible for women, men, gender non-conforming, and LGBTI people.

- Avoid categorising contraceptives as 'reliable' and 'unreliable'.

- Give a full list of contraceptive options that can be used.

- Don't forget that participants may want to protect themselves from both pregnancy and HIV/STIs during the trial – make sure the wording you use acknowledges that and include condoms (and/or the use of condoms plus another method as dual protection) in any lists of contraceptives.

- Specify that contraceptive use is only a requirement for men and women who are having heterosexual sex.

- Make it clear that no contraceptive use is required between adults of the same sex.

- Understand that desires around pregnancy are fluid and change over time. Use non-judgemental language about pregnancy in patient information and throughout the trial.

Meaningfully engaging communities: the perspective of the 4M Mentor Mother Network's Peer Mentor Mother Researcher

The principle of GIPA⁵⁰ (the Greater Involvement of People Living with HIV/AIDS) was the formalisation of the value of lived experience and community involvement in research. It is rooted in the fundamental human right to participate in research⁵¹ and ensures relevant policies and practice. Previously, the Denver principles⁵² drawn up in 1983 by people living with HIV, provided the foundation for the rights, self-empowerment, self-determination, and involvement of people living with HIV in the HIV response and was the base from which GIPA and the parallel concept of the Meaningful Involvement of Women living with HIV and AIDS HIV (MIWA) were developed. In the early 2000s, the International Community of Women living with HIV (ICW) developed a participation tree as a visual guide⁵³ to help researchers and women living with HIV identify the true definition of involvement. 'Involvement is respectful engagement with and learning from communities'.⁵⁴

Furthermore, the 2017 World Health Organization (WHO) Consolidated Guideline on SRHR of women living with HIV, which was developed in collaboration with women living with HIV, recommends that

Research about women living with HIV should be conducted with, by and for women living with HIV, as equal research partners. Research that is pursued and funded in this area should include justification for why it is important to women living with HIV. (6.2.1)⁵⁵

Ultimately, meaningful involvement is an SRHR issue,⁵⁶ and there are numerous examples of good practice of meaningful involvement of women in research.⁵⁷⁻⁶²

Some challenges to meaningful involvement

Some of the challenges of meaningfully involving women in trials include a lack of awareness and commitment to meaningful involvement by both academic or clinical researchers and community.⁶³⁻⁶⁵ Moreover, while there can be support for meaningful involvement in theory, there can be a reluctance to adopt community input in practice.

Another barrier is women's capacity to be involved, often determined by multidimensional psychosocial intersections which become a barrier. For example, intersections such as caregiving responsibilities can take priority over-involvement.

While there is value in the diversity of experiences, there is an ongoing challenge of skilled and unskilled involvement. Lack of investment in capacity building of the unskilled means the odds are in favour of the skilled, leaving out unskilled women's voices.

HIV stigma makes it challenging to acknowledge some women's contributions in public spaces due to the fear of being recognised. Some ways around it include the use of pen names and working collaboratively with individuals and organisations for robust confidentiality processes and policies.

Although community groups have systems in place to obtain collective responses from the community, it can be challenging to adequately capture a representative view when a single community member is saddled with the responsibility of representing a community group.

Geographically, meaningful involvement opportunities are concentrated in cities and less in rural areas. This in turn means that the bias is more heavily weighted towards bigger cities when it comes to representation and engagement.

A lack of monitoring and evaluation of meaningful involvement means lost opportunities for collection of evidence, reflection, and learning.

Additional barriers include dwindling numbers of current peer researchers and a lack of investment by stakeholders to develop new peer researchers. This means that the small numbers of researchers can end up stressed and burnt out from over-involvement. It is helpful to have systems and resources available to support them through involvement, for their own wellbeing.

The lack of commitment to making women's involvement a priority and the challenging funding terrain can limit the capacity of both women and researchers to achieve meaningful involvement.

What works to increase willingness of women to participate in HIV research?

Ensuring that women living with HIV are in leadership and decision-making roles enables us to keep our priorities in focus.^{63–65} Involvement in research is meaningful when it is from start to finish as equal partners, from ethical review boards to co-reviewers, co-authors, and co-presenters.⁶⁶ The 4M Network of Mentor Mothers have developed useful guidance for researchers wishing to meaningfully engage with Mentor Mothers and other women living with HIV, in clinical trials and other studies.^{67,68}

It is also important to recognise and support diverse experiences and models of involvement including accessible opportunities, working with women in all our diversity.

Investment by funders in sustainable training and mentoring of women in collaboration with grassroots organisations is also an integral part of a meaningful involvement process. This will enable us to develop our capacity. The provision of supportive environments will also enhance our involvement. These include family-friendly clinic times, transport, and childcare.

A recognition of the value women provides with respectful remuneration, as an integral part of the meaningful involvement process is also key. This can include easy expense or payment processing systems that are paid upfront.

There should also be sustainable investment in long-term relationship building that enables trust and collaborative engagement between the women and academic or clinical co-researchers.

Innovation and flexibility to meet women's changing needs and priorities aids the process too. Community involvement can be motivated by translation of research findings into practice and policy that is relevant.⁶⁹

There is also a continued need to reach out to rural areas, working in close collaboration with existing community organisations to develop meaningful relationships with women who are more isolated.

Robust monitoring and evaluation of meaningful involvement including disaggregation of data, cultural sensitivity, and inclusion to ensure

adequate representation of women in all our diversity is essential for collation of evidence.

Grassroot organisations have an established culture of meaningful involvement and responsiveness to women's priorities. Funders and researchers can learn from and adopt these tried and tested and effective strategies.

What also works well is sustainable unrestricted investment of researchers and funders in women's grassroots organisations, which develops the capacity of women to be involved.

Ultimately, meaningful involvement requires a multidimensional, holistic approach, which includes addressing the psychosocial intersectional issues that focus on our quality of life and inevitably affect community members' ability to be involved.⁵⁷

Ensuring our SRHR and our priorities: the perspective of a global HIV, gender, and SRHR activist

The meaningful involvement of women living with HIV in clinical trials as a minimum standard requirement is another part of the jigsaw of global reforms needed for women living with HIV to achieve their SRHR. Indeed, their right to involvement has long been stated. The 1948 Universal Declaration of Human Rights⁵¹ states:

'Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits'. Article 27.1.

In the 2017 WHO Guideline on SRHR of women living with HIV, also cited above,⁵⁵ Section 6.2.2, regarding study design, states

'Researchers should contextualize their research within the range of relevant existing health services, resources and actors, the relationships between actors, and the variety of influences across the social ecological framework that may need to be addressed to facilitate beneficial outcomes (175). While not every study can cover all elements of a topic, studies should endeavour to consider both clinical and behavioural elements of SRHR and HIV and, at a minimum, to consider the limitations of their work in the absence of either. In writing up the research, the authors should fully describe the interventions

and the context in which they operate so that they can be transferred to other settings, with appropriate adaptations as needed to ensure the highest probability of success’.

Other, more recent documents, also advance these perspectives. For example, the 2020 Respectful Maternity Care Charter,⁷⁰ based on numerous preceding covenants and charters, states

‘6. Everyone has the right to healthcare and to the highest attainable level of health. No one may prevent you or your newborn from getting the healthcare needed or deny or withhold care from either one of you. You and your newborn are entitled to the highest quality care, provided in a timely manner, in a clean and safe environment, by providers who are trained in current best practices’.

It can clearly be argued that the ‘highest attainable level of health’ prerequisites women’s meaningful involvement in clinical trials in order to obtain the ‘highest quality care, provided in a timely manner’.

In September 2021, the Royal College of Obstetricians and Gynaecologists (RCOG), the International Federation of Gynaecology and Obstetrics and (FIGO), and The American College of Obstetricians and Gynaecologists published a Childbirth Bill of Rights.⁷¹ This states

‘All countries have an obligation to respect, protect and fulfil the right to health, including maternal health. Maternal health encompasses the health care dimensions of pre-pregnancy, prenatal and postnatal care. Together, they ensure a positive and fulfilling experience and wellness during pregnancy, at the time of birth and during parenting . . . Access to surgical interventions, blood products, water, oxygen, effective medications and treatments to provide appropriate and safe care to all pregnant women’.

Although there is no specific mention of clinical trials, it could be argued that this statement too prerequisites women’s meaningful involvement in clinical trials in order to obtain ‘access to effective medications and treatments’, especially in the context of HIV, where women are expected to take ARV medication, both for their own health and wellbeing and to protect their babies from HIV acquisition.

This last point is a key area of concern to women living with HIV since, over the years, there has been significant global emphasis on ‘elimination of mother to child transmission’ (eMTCT) programmes, which have essentially depended on women taking ARVs throughout pregnancy, even when women have not been included in clinical trials. From the perspective of women living with HIV, there has been far too much emphasis on women taking ARVs during pregnancy primarily to protect their sexual partners and babies from acquiring HIV, rather than for their own intrinsic health and wellbeing. Chitembo *et al.*⁷² in 2012 stated:

‘What is perhaps most disappointing... is the Global Plan’s narrow focus on disease prevention rather than on a holistic right to health for all concerned. Its overall focus is on perinatal HIV prevention, rather than on an affirmation of health, autonomy, life and rights for all, women and babies alike’.

It has felt as if women living with HIV have been urged to take ARVs during pregnancy, even when, *because* of potentially becoming pregnant, they have not been involved in clinical trials at all, for the sake not so much of their *own* health, but that of their unborn babies.^{32–34} Over the years, eMTCT programmes have contributed to much structural violence in healthcare settings, where women have been subjected to blame and shame during pregnancy and coerced and forced sterilisations.⁷³ The historical dimensions of such programmes and the concomitant exclusion of women from health and social care processes relating to pregnancy and childbirth are explained in more depth in a 2021 book chapter by members of the 4M Mentor Mothers Network Steering Group.⁷⁴ In addition, a 2020 article by 4M spelt out the importance of shifting the paradigm from an emphasis on ‘eMTCT’ programming to instead ensuring the SRHR (or ‘eSRHR’) of women living with HIV throughout the pregnancy journey, to achieve healthy outcomes both for women and for their babies.⁷⁵

Of course, the meaningful involvement of women living with HIV in *all* clinical research is important, not just during pregnancy. But it is perhaps especially understandable that researchers have wanted to make sure that women do not experience any trauma echoing the use of thalidomide during pregnancy in the early 1960s.⁷⁶ Yet it could be argued that a double standard has emerged in the context of women, HIV, and pregnancy,

whereby women have felt especially singled out for aggressive medical interventions during pregnancy, with the main focus on stopping onward HIV transmission to their children and partners at all costs. So, rather than excluding women living with HIV who are pregnant from ARV use entirely, women when pregnant have felt compelled to take ARVs, with minimal involvement in clinical trials, for the sake of their babies, while experiencing violations of their own confidentiality and safety.^{73,77,78} This can often feel especially stressful because women are wanting to do their utmost to protect their unborn babies and can therefore often avoid even taking non-prescription painkillers or decongestants, for fear of damaging the foetus in some way. So the requirement to take ARVs in pregnancy demands especial respect, explanation, and support from healthcare providers, when it clearly contradicts the normal warning on patient information sheets to avoid any medication during pregnancy.

We would like to hope that the lack of women's meaningful involvement in clinical trials has been a situation of omission rather than commission, but recent efforts to unpack these discrepancies and to ensure that women living with HIV *do* have these opportunities is both highly welcomed and long overdue.

It also follows from this that if we increasingly recognise women's rights to informed choice around meaningful involvement in trials, this should also be open to women living with HIV across the life course and outside the context of pregnancy, to bring women in all their diversity in line with the rights to access to clinical trials experienced by white men.⁷⁹ Many women living with HIV never get pregnant or want to do so – and yet there has consistently been far less emphasis on healthcare support for women outside pregnancy in the context of HIV.

A move by clinical researchers to involve women living with HIV meaningfully in clinical trials would also be a step towards overcoming the traditional approach of researchers that *any* involvement of 'trial subjects' must be avoided at all cost, in order to avoid bias in research. Yet as other work by women living with HIV and partners has repeatedly shown, there is a chronic need to feed diverse community perspectives into evaluation and research frameworks and to broaden what constitutes the evidence base.⁸⁰ Far from 'biasing' research

findings, it will make them much more relevant and useful to the women themselves who may be using the medications. Calling for meaningful involvement of women living with HIV in clinical trials should *not* be seen as a call to jeopardise or abandon the technique of double blinding in trials, which of course applies even to the clinicians, who do not know which individual is on which drug. This component should certainly stay intact. Yet at present, the fear of bias is ruling the whole process. A change in policy and practice regarding women's meaningful involvement in trials will be a much-welcomed shift which will be to the benefit not only of women themselves but to all genuinely committed to their long-term care and wellbeing.

What's in it for women? What are the benefits of including women? The perspective of a community research and treatment literacy advocate

Women living with HIV should be effectively and meaningfully involved in clinical trials and other studies because it is key to their good health, vitals, and it makes sense; as there is no point in conducting clinical trials that are not relevant or useful or responsive to our/participant needs; and because they have the skills, expertise, and lived experience to make a very positive contribution to trials, both before, during, and on completion.

It could be argued that this is true for men too and for minority and/or complex patient groups. This is indeed true. However, the reality is that, until now, the default, sometimes unwritten, assumptions are that (a) patients should only be involved in clinical trials as objects of study, so as not to 'bias' the research; (b) if more involved than this, then they are usually educated white men in high-income countries; (c) that the medication under trial is administered in doses appropriate to men's average weights and heights. Since 53% of adults living with HIV worldwide are women; since the majority of them live in lower- or middle-income countries and are women of colour; and since there is growing recognition of gender – and race – disparities in access to health care globally,^{81,82} the time is now to redress these imbalances and ensure maximum involvement of *all* those affected in clinical trials – including, and particularly, women.

There are many benefits to women being involved, both for the individual and the community. This

is perfectly embodied by the term Ubuntu, a South African term meaning ‘we are who we are because of other people’. It is a quality that includes the essential human values of compassion and humanity.

When women get involved, they benefit at a personal level; they benefit the community (of their peers) now as well as the community living with HIV who will come after them, therefore, creating a positive knock-on effect, from the personal to the global. In addition to that it can create a true sense of altruism: the knowledge that their involvement will, in the future, support and benefit other women living with HIV.

It is important for women to participate and to be included in clinical trials so that the medicines they and their peers are going to take are tested on women and, as such, benefit women.

Involving women in trials early enables them to shape trials or other studies, and ensures that they are both appealing and of benefit to them.

On a personal level, other benefits for women being involved include regular monitoring. This can also have further benefits because other underlying co-morbidities, issues, and ailments can be picked up and addressed earlier.

Being involved enables women to know what is involved in being in a clinical trial. Women learn and those who wish to, can share the learning, advocate for more inclusion and encourage their peers to get involved too.

Our bodies are different from men, both biologically and physically. Women experience greater changes biologically and socially; our bodies change dramatically from puberty, during our reproductive years, and through the menopause. There are also significant social and medical differences between men and women, and we need more gender-specific data. The more women get involved, the more of this quality data are generated, which works towards better health outcomes specifically for them.

Historically, women are under-represented in clinical trials. A concerted effort to increase women’s involvement therefore ensures more and better representation of women.

The more quantity of women are involved, the more meaningful involvement will become part and parcel of clinical and other studies. This is, in turn, a win–win for all stakeholders.

Women living with HIV and their allies have been advocating for more inclusion of women over the years; and they continue to advocate for a shift in the current paradigm from one of presumptive exclusion towards fair inclusion. It is critical that all stakeholders work together to enact this shift in paradigm from the exclusion of women (including pregnant and lactating women), in clinical trials, to inclusion. The will to involve women is there from stakeholders, as is evidenced by recent trials. These include: The GRACE study,^{28,81} The WAVES study,²⁹ and the ARIA³⁰ study, all of which had 100% women participants. The SALSAs study,⁸³ presented at the International AIDS conference in July 2021 had 44% women participants. A significant and welcome shift in engaging women in clinical trials.

Being involved in clinical trials enables women to make informed choices and provides choices for other women living with HIV. It is therefore important that from the outset, women are provided with information about risks and benefits of being involved, so that they can make informed choices.

The more women are involved, the more women also become familiar with and build up their treatment/and research literacy. And the more they learn, the more they can then share with their peers and wider communities of women living with HIV. This in turn goes a long way to ensuring better health outcomes for women living with HIV.

There are a number of ways in which women living with HIV can be meaningfully involved in clinical trials and other studies

Beyond being involved as clinical trial participants, clinical trials themselves and the work of researchers can also benefit from including women throughout the life-cycle of trials/studies.^{84,85}

At the start:

Women can help researchers to ask the right question/s in the right way and to ensure that

research is relevant not only to clinicians and researchers, but also to the community

They can participate in discussions about ideas for future projects/analysis plans.

During the study set up:

They can support to select the appropriate study name/acronym.

They can participate in discussions around design and content.

They can pilot questionnaires and review patient information sheets, ensuring that the language is appropriate and sensitive.

They can co-author and review study material (grant applications, papers, abstracts etc).

During the study:

They can participate as key members of the project management team, and thereby help monitor progress, identify problems, and find solutions.

They can help to identify potential barriers to engagement, particularly for traditionally underserved groups and help to ensure that engagement procedures are sensitive to participant needs.

They can help to ensure that engagement procedures are sensitive to participants' priorities.

They can write and suggest changes to patient information leaflets and consent documents to improve and increase clarity and increase participation.

They can suggest ideas for information that can be shared with participants which might encourage participation.

They can conduct focus group discussions.

They can support website design and review website materials.

At the end of the study:

They can provide support with the dissemination of research findings to wider audiences.

They can co-produce community Frequently Asked Questions (FAQs) documents.

They can work closely with the study team to co-author papers and ensure that papers are appropriately worded.

They can and should be named as co-authors.

They can co-present papers at relevant meetings and conferences.⁶⁶

More generally, women living with HIV can be powerful advocates for continuation of studies or greater funding. They can support educational work to increase awareness of biases that may be present, both among researchers and community. And they can conduct patient surveys for research priorities for other potential sensitive areas.

Women living with HIV are also thirsty to learn: they also want to advance their own academic and research careers as collaborative researchers, and to improve the lives of other women living with HIV in the process. Being meaningfully involved in these processes also offers an ideal opportunity for those who want to, to take their learning further.

All this is possible, has happened, and continues to happen in some studies. But we need more.

As long as women are given the right information, including the risks and benefits, and as long as strategies are put into place to address any potential risks that may come up while women are on trials, then women (whether they are pregnant or planning to start a family or not), should be given the opportunity to choose whether or not to be involved in clinical trials.

Conclusion

This article has provided perspectives from a variety of different community, medical, and advocacy stakeholders, all of whom advocate the meaningful involvement of women living with HIV in clinical trials.

- Consultants in HIV medicine and sexual health highlight the clear clinical benefits of women's meaningful involvement in clinical trials, both for clinicians and the women in their care alike.
- A woman living with HIV who works in a busy London clinic as a peer navigator notes how few trials focus specifically on

women's issues, and describes the complex challenges facing women living with HIV, which are still not sufficiently researched or supported. Women's greater involvement in trials – and more trials focusing on women's experiences of HIV – could contribute positively to their quality of life, as well as to their ability to keep taking ARVs.

- A gender and health policy analyst discusses how trial contraceptive stipulations can feel intrusive and can assume that all women are fertile, having heterosexual sex and may get pregnant. She unpacks the nuances of women's potential issues regarding contraception and dual protection, and offers a list of recommendations for trial designers to consider.
- A community-based peer researcher calls for women's meaningful involvement throughout the research process, from ethical review board applications to co-authoring and co-presenting findings. To ensure multidimensional, holistic involvement, recommendations include investment in women's grassroots organisations to build long-term trusting relationships, capacity building for them to develop relevant skills, ensuring diversity of lived experiences, including ethnic, age-related and urban/rural diversity, monitoring and data disaggregation of all these, recognition of all the diverse commitments to family that many women have in trial design (such as family-friendly clinic times) and the need to mentor younger peer researchers.
- A global gender and HIV activist describes global documents which highlight and/or prerequisite women's rights to meaningful involvement in all research that affect their lives. She explores the tension between a focus on women's health to protect their babies and/or partners from acquiring HIV, and 4MNet's advocacy position on ensuring women's SRHR (eSRHR) rather than the 'eMTCT' mantra. She describes the stress for women in having to take ARVs during pregnancy when in all other contexts, women are strongly advised against any medication during pregnancy. There is far more to gain through women's meaningful involvement in trials than there is to lose through any 'bias', especially when the

core principle of double blind trials means that even clinical researchers cannot identify individual trial participants.

- Finally, a community research and treatment literacy advocate highlights the need to redress the historical imbalance in trial involvement, especially since the majority of adults with HIV globally are women. She describes the compound benefits at personal, community, and global levels, now and in the future of trial involvement, adding that a sense of altruism also adds to women's willingness to take meaningful part. She emphasises the importance of making medicines fit for women, rather than assuming that all respond to medicines in the same way. Women who are meaningfully involved in trials can become powerful advocates for more funding for such trials. She calls for all women to have their rights to informed choice to be involved to be upheld.

In sum, all the authors have provided their own perspectives on why they recommend meaningful involvement of women living with HIV in clinical trials. If not now, when?

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