Perspectives on the use of modelling and economic analysis to guide HIV programmes in sub-Saharan Africa

The Modelling to Inform HIV Programmes in sub-Saharan Africa (MIHPSA) Working Group\*

\*Full list of Working Group members:

Paul Revill, Ajay Rangaraj, Albert Makochekanwa, Amon Mpofu, Andrea L. Ciaranello, Andreas Jahn, Andrew Gonani, Andrew N. Phillips, Anna Bershteyn, Benson ZwiZwai, Brooke E. Nichols, Carel Pretorius, Cliff C. Kerr, Cindy Carlson, Debra Ten Brink, Edinah Mudimu, Edward Kataika, Erik Lamontagne, Fern Terris-Prestholt, Frances M. Cowan, Gerald Manthalu, Gemma Oberth, Gesine Mayer-Rath, Iris Semini, Isaac Taramusi, Jeffrey W. Eaton, Jinkou Zhao, John Stover, Jose Antonio Izazola Licea, Katharine Kripke, Leigh Johnson, Loveleen Bansi-Matharu, Marelize Gorgens, Michelle Morrison, Newton Chagoma, Owen Mugurungi, Robyn M. Stuart, Rowan Martin-Hughes, Rose Nyirenda, Ruanne V. Barnabas, Sakshi Mohan, Sherrie L. Kelly, Sibusiso Sibandze, Simon Walker, Stephen Banda, R. Scott Braithwaite, Thato Chidarikire, Timothy B. Hallett, Thoko Kalua, Tsitsi Apollo, Valentina Cambiano

Institutions:

Centre for Health Economics, University of York, York, UK (Prof. P Revill MSc, N Chagoma MSc, S Mohan MSc, S Walker MSc); World Health Organization, Geneva, Switzerland (A Rangaraj, MBBS); Department of Economics & Development, University of Zimbabwe, Zimbabwe (Prof A Makochekanwa PhD, B Zwizwai MSc); National AIDS Council of Zimbabwe, Harare, Zimbabwe (A Mpofu, I Taramusi PhD); Massachusetts General Hospital, Boston, MA, USA; Harvard Medical School, Boston, MA, USA (A L Ciaranello); HIV Unit, Ministry of Health, Lilongwe, Malawi (A Jahn PhD, R Nyirenda MSc, T Kalua MD); National AIDS Council of Malawi, Lilongwe, Malawi (A Gonani MD); Institute for Global Health, University College London, London (Prof. A N Phillips PhD, Loveleen Bansi-Matharu PhD, Valentina Cambiano PhD); New York University School of Medicine, New York, NY, USA (A Bershteyn PhD, Prof R S Braithwaite MD); Department of Global Health, School of Public Health, Boston University, Boston, MA, USA (B E Nichols PhD, G Mayer-Rath PhD), Avenir Health, Glastonbury, CT, USA (C Pretorius PhD, J Stover PhD, K Kripke PhD); Burnet Institute, Melbourne, VIC, Australia (C C Kerr PhD, D Ten Brink MD, R Martin-Hughs PhD, S L Kelly PhD), Independent (C Carlson MSc, G Oberth PhD); Department of Decision Sciences, University of South Africa, Pretoria, South Africa (E Mudimu PhD); East Central and Southern Africa Health Community, Arusha, Tanzania (E Kataika MSc, S Sibandze MSc); Joint United Nations Programme on HIV/AIDS, Geneva, Switzerland (E Lamontagne PhD, Prof. F Terris-Prestholt PhD, I Semini PhD, J A Izazola-Licea PhD); Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London (Prof. F Terris-Prestolt PhD); Department of International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK (Prof. F M Cowan MD); Centre for Sexual Health and HIV AIDS Research (CeSHHAR), Harare, Zimbabwe (Prof. F M Cowan MD); Department of Planning and Policy Development, Ministry of Health, Lilongwe, Malawi (G Manthalu PhD); Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (G Mayer-Rath PhD); MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK (J W Eaton PhD, Prof. T B Hallett PhD); The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland (J Zhao MD); School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa (L Johnson PhD); Global HIV/AIDS Program, The World Bank Group, Washington, DC, USA (M Gorgens MPH); Bill & Melinda Gates Foundation, Seattle, WA, USA (M Morrison PhD); Ministry of Health and Child Care, Harare, Zimbabwe (O Mugurungi PhD, T Apollo PhD, S Banda MSc); Department of Mathematical Sciences, University of Copenhagen, Copenhagen, Denmark (R M Stuart PhD); Departments of Global Health, Medicine and Epidemiology, University of Washington, Seattle, USA (R V Barnabas MD); National Department of Health, Pretoria, South Africa, Pretoria, South Africa (T Chidarikire, MD).

Author contributions:

Conceptualisation of the paper and substantial input to writing: all authors. Overall study leads: PR, ANP. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the authors' institutions.

Role of the funding source:

The Viewpoint was coordinated by PR and AP, who are funded through the HIV Modelling Consortium, with financial support received by the Bill & Melinda Gates Foundation. The funder had no role in the ideas expressed or in the writing of the manuscript.

Declaration of interests:

We declare no competing interests

Summary:

HIV modelling and economic analyses have had a prominent role in guiding programmatic responses to HIV in sub-Saharan Africa. We reflect critically how the HIV modelling field might develop in future. We argue for HIV modelling to be more routinely aligned with national government and ministry of health priorities, recognizing their legitimate mandates and stewardship responsibilities, for HIV and other wider health programmes. We also place importance on an environment existing in which collaboration between modellers, and joint approaches to addressing modelling questions, becomes the norm rather than exception. Such an environment can accelerate translation of modelling analyses into policy formulation because areas where models agree can be prioritized for action, whereas areas over which uncertainty prevails can be slated for additional study, data collection and analysis. We also argue the need for HIV modelling to increasingly be integrated with the modelling of health needs beyond HIV, particularly in allocative efficiency analyses, where focusing on one disease over another may lead to worse health overall. Such integration may also enhance partnership with national governments whose mandates extend beyond HIV and to all of health care. Finally, we see a need for there to be substantial and equitable investment in capacity strengthening within African countries, so that African researchers will increasingly be leading modelling exercises. Building a critical mass of expertise, strengthened through external collaboration and knowledge exchange, should be the ultimate goal.

Main manuscript:

HIV treatment and prevention programmes have contributed to impressive increases in national life expectancies in sub-Saharan Africa (SSA). For instance, life expectancy has increased from 45 years in 2000 to 65 years today in Malawi, from 45 to 62 years in Zimbabwe, and 56 to 64 years in South Africa.1 Despite this significant progress, almost 1 million new HIV infections are still occurring each year in the region.2 HIV policymakers and programme planners, particularly those working at national levels (i.e., for ministries of health and national AIDS commissions), face challenging economic choices over the allocation of limited resources across treatment and prevention interventions, including prioritization geospatially and amongst heterogeneous populations. Mathematical disease modelling can guide resource allocation and has played an important role in shaping HIV policies, such as the move towards providing ART for all people living with HIV,3-4 the introduction of dolutegravir5-6 and scale-up of voluntary medical male circumcision.7-8 However, to date, there has been relatively little critical reflection on its role within the institutional arrangements that characterize HIV responses in SSA.

Funding environments for the delivery of HIV services in SSA are complex and fragmented. Commitments from country governments in SSA to sustain their own HIV response have increased over the years;9 in all countries they usually fund health care worker and facility infrastructure costs, for instance, as well as provide managerial oversight, stewardship and coordination. Nevertheless, there is a substantial reliance on overseas development assistance (ODA) and this calls into question how modelling analyses can best be conducted and used, given the differing roles and mandates of national public authorities and their external partners. In 2019, funding from international channels accounted for 59% of total HIV spending in east and southern Africa and 64% in west Africa.10 The two largest sources of ODA for HIV in SSA are the Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) and the United States government’s President’s Emergency Plan for AIDS Relief (PEPFAR) programme, which together accounted for 85% of the $6.795 billion spent in 2019.11 Other international funders (e.g. France, the United Kingdom and the Netherlands) also make substantial contributions.

The high reliance of HIV programmes in SSA on ODA comes with risks, given the interdependencies between the organizations involved in the funding and delivery of HIV services. Development assistance has plateaued since 2010 and there are signs of reduced commitments to HIV.11 This has led to talk of an ‘HIV funding transition’ in which African countries would increasingly fund HIV services through domestic financing. Whether this transition happens and the speed at which it may take place are still uncertain, but it could have widespread ramifications for how HIV services are delivered, e.g., a shift away from delivery by international non-governmental organizations towards nationally-run, public systems. Such a shift would require countries to take on increased responsibility for HIV programme delivery in the face of a myriad of other health challenges.

It is necessary to consider who should be responsible for the generation and use of evidence on resource allocation, including through modelling, in this context. Stakeholders involved in funding and planning HIV programmes in SSA have a strong interest to ensure their resources are spent to generate the greatest possible beneficial impacts. Although the goals for all major organizations working on HIV in SSA appear to be broadly the same (i.e. to reduce HIV incidence and the adverse health and welfare consequences of HIV), what this means for programme planning can differ depending upon what the specific objective used in modelling is. Models can, for instance, provide evidence to minimize HIV-related deaths, minimise HIV incidence, maximize equity of access to services, minimise spending to reach a target or maximize disability-adjusted life years (DALYs) averted in a population from some given level of budget spend. Each of these objectives would be considered important to all organizations working on HIV in SSA, but not all can be met simultaneously. Ultimately the decision on prioritization between objectives which are not all attainable introduces subjective judgements that should necessarily be made through a process of deliberation amongst local stakeholders, informed by the modelling evidence. The meaningful involvement of affected populations in such deliberations is important.

Organizations that use models to inform their own planning processes do so with slightly differing purposes. The Global Fund, for instance, supports countries to develop national strategic plans (NSPs) on which to base their funding requests. It explicitly recommends that modelling is used to determine an “allocatively efficient” configuration of a country’s HIV programme.12 This can comprise health systems requirements, such as staffing and infrastructure needs, which support many interventions, as well as direct funding to treatment and prevention interventions. Funding allocations from PEPFAR are laid out annually in Country Operational Plans (COPs).13 These are guided by a longer-term strategic plan,14 informed by modelling, and tend to be highly specific in what interventions are funded and where. UNAIDS is leading the global effort to end AIDS as a public health threat by 2030 and facilitates inclusive processes at country-level, to estimate health burdens, track the status of programmes and monitor progress11,15; a new strategy emphasizes a people-centred approach and addressing of inequalities.16 The UNAIDS intervention coverage targets are informed by modelling.17 The World Bank is also concerned with allocative efficiency across all HIV-related spending, with bundles of interventions differing widely by country. The WHO, although it relies mainly on clinical and service delivery data in the development of its clinical guidelines, is increasingly incorporating insights from modelling studies into its global guidelines, especially in relation to cost-effectiveness.18,19

At the centre of these varied activities are country governments, in particular ministries of health and national AIDS commissions, that face often severe resource and human capital constraints but have to engage in grant applications and numerous planning and reporting exercises to meet the requirements of their diverse funders. They receive support from their funders and other technical partners, but as mentioned above each organization inevitably has slightly differing aims. Country government authorities are recognized through international agreements and conventions as ultimately having the mandate to make decisions on setting policy and resource allocation. The Paris Declaration on Aid Effectiveness and Accra Agenda for Action, for instance, emphasize national ownership of policy formulation, mutual accountability between international funders and host governments, and a focus on results.20 Most HIV models used in guiding policy in SSA have been developed by research teams based in universities or other research institutions, mostly in high-income countries. While some country governments in Africa are already increasing their capacity to use modelling for policy formulation, further development of these capabilities is necessary to fulfil the vision of the Paris Declaration.

HIV modelling needs to be grounded in the policy choices faced by countries, led by local health authorities, and directed toward issues of greatest consequence for population health and well-being. However, local health authorities currently have limited capacity to fund, commission, conduct, coordinate, and ultimately use modelling analyses. One consequence of this limited capacity has been a relatively narrow focus of modelling analyses on addressing questions set by international funders, typically on HIV programs and their HIV-specific goals, rather than addressing questions arising from country-level policymaking processes. Such questions could include how to better integrate funding and delivery mechanisms for HIV services with wider health care concerns and systems planning, as well as further exploration of the distributional and equity consequences of different resource allocations. Modelling relies upon the availability and quality of underlying data and international efforts to collate data on model inputs, such as on intervention costs, can be beneficial for constructing models. When data quality is poor, techniques such as expert elicitation to inform model parameters can be used.21 Moreover, where there are major uncertainties due to lack of data, modelling can highlight where additional data would be most valuable to strengthen the reliability of modelling results to better inform policymaking.22

The Sustainable Development Goals (SDGs), set for 2030 and towards which all countries are now working, include Ending AIDS as a public health threat (SDG3.3) and also a commitment to Universal Health Coverage (SDG3.8), defined as access to a basic package of health care to which all citizens are entitled. To meet both objectives requires sustaining and expanding the successful response to HIV and also ensuring this aligns with and contributes to wider expansion of effective health services to all in need.

The 2021 Political Declaration on HIV and AIDS includes commitments to accelerate integration of HIV services into universal health coverage (UHC) and strong and resilient health and social protection systems, synergistic with other SDGs.23 The Global Fund and PEPFAR have also developed policies to support these efforts and their funding for health systems strengthening (HSS) has more than doubled between 2010 and 2017.9 The goals of UHC and Ending AIDS must be met in tandem – bringing HIV epidemics under control helps to limit budgetary demands, freeing up resources for investments towards UHC, and ensure the long-term financial sustainability of HIV spending. Modelling can play an increasingly prominent role in HIV programme design, but this also needs to be done in cognizance of other health needs. If the right decisions are made, this could lead to HIV services becoming more efficient and better integrated with other health services, supporting patient-centred care and reducing inequalities. Steps in this direction must be evidence-based and careful to ensure that the successes seen in HIV programmes to date are not compromised in the process of integration with broader healthcare delivery systems. They could be accompanied by similar changes in other areas of health care that have been reliant on ODA, such as malaria.24

For modelling to contribute most effectively to HIV programme design and UHC in future, in our view, requires four things. First, that HIV modelling is more routinely aligned with and ideally emerges from national government and ministry of health priorities, recognizing their legitimate mandates, and based on an understanding of country needs. This should be conducted according to established best practices25 and use recognized taxonomies of interventions.26 Even if modelling continues to be predominantly commissioned and funded internationally, in the short term, it is imperative that it is focused on issues emanating from the country perspective. Second, that an environment exists in which collaboration between modellers and joint approaches to addressing modelling questions becomes the norm rather than exception. Such an environment can accelerate translation of modelling analyses into policy formulation because areas where models agree can be prioritized for action, whereas areas over which uncertainty prevails can be slated for additional study, data collection and analysis. Third, that HIV modelling is integrated with the modelling of health needs beyond HIV, particularly in allocative efficiency analyses, where focusing on one disease over another may lead to worse health overall. This integration may also enhance partnership with national governments whose mandates extend beyond HIV and to all of health care, as reflected in national health sector strategic plans, other national policies and the international commitment to UHC. There is also potential for strengthened regional partnerships within SSA. Fourth, there needs to be substantial and equitable investment in capacity strengthening *within* African countries, so that African researchers will increasingly be leading modelling exercises. In addition to being better aligned to local health challenges, African-led studies are also likely to resonate more and lead to better uptake by local policymakers.27 This can only happen with the commitment of all key stakeholders and, crucially, large and sustained funding. Building a critical mass of expertise, strengthened through external collaboration and knowledge exchange, should be the ultimate goal.

HIV programmes and policy needs are best understood locally, and evidence-informed policy formulation needs to be a continuous endeavour led by local actors. We believe our suggestions, if implemented, would represent a step-change in efforts to attain improvements in population health and well-being in countries most adversely affected by HIV. Similar approaches could also be adopted in and have been advocated for other areas of health care, especially those that are reliant on ODA, such as malaria.22 This Viewpoint has been developed collaboratively between leading practitioners of HIV modelling and those working on HIV policy focused on SSA, but the balance of authorship is heavily balanced towards northern institutions. This is indicative of the challenges faced but also the willingness of key actors to work in better ways. It is in the interest of all that, in future, leadership of analysis and policy decisions that respond to the challenges posed by HIV are increasingly centred in Africa.

**References**

1. United Nations, Department of Economic and Social Affairs, Population Division, World Population Prospects 2019 - Special Aggregates, Online Edition. Rev. 1. 2019. [cited 2021, Oct 23] Available from: [https://population.un.org/wpp/Download/Files/3\_Indicators%20(Special%20Aggregates)/EXCEL\_FILES/1\_EconomicTrading/Interpolated/WPP2019\_SA1\_INT\_F01\_ANNUAL\_DEMOGRAPHIC\_INDICATORS.xlsx](https://population.un.org/wpp/Download/Files/3_Indicators%20%28Special%20Aggregates%29/EXCEL_FILES/1_EconomicTrading/Interpolated/WPP2019_SA1_INT_F01_ANNUAL_DEMOGRAPHIC_INDICATORS.xlsx)
2. UNAIDS. “UNAIDS Data 2020”. 2020. [cited 2021, May 2] Available from: <https://www.unaids.org/en/resources/documents/2020/unaids-data>
3. Granich, R.M., Gilks, C.F., Dye, C., De Cock, K.M. and Williams, B.G., 2009. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *The Lancet*, *373*(9657), pp.48-57.
4. Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, Hontelez JA, Humair S, Kerr CC, Klein DJ, Mishra S. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. The Lancet Global Health. 2014 Jan 1;2(1):e23-34.
5. Dugdale CM, Ciaranello AL, Bekker LG, Stern ME, Myer L, Wood R, Sax PE, Abrams EJ, Freedberg KA, Walensky RP. Risks and benefits of dolutegravir-and efavirenz-based strategies for South African women with HIV of child-bearing potential: a modeling study. Annals of internal medicine. 2019 May 7;170(9):614-25.
6. Phillips AN, Venter F, Havlir D, Pozniak A, Kuritzkes D, Wensing A, Lundgren JD, De Luca A, Pillay D, Mellors J, Cambiano V. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. The Lancet HIV. 2019 Feb 1;6(2):e116-27.
7. Gray RH, Li X, Kigozi G, Serwadda D, Nalugoda F, Watya S, Reynolds SJ, Wawer M. The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. Aids. 2007 Apr 23;21(7):845-50.
8. Kripke K, Opuni M, Schnure M, Sgaier S, Castor D, Reed J, Njeuhmeli E, Stover J. Age targeting of voluntary medical male circumcision programs using the Decision Makers’ Program Planning Toolkit (DMPPT) 2.0. PloS one. 2016 Jul 13;11(7):e0156909.
9. Micah AE, Su Y, Bachmeier SD, Chapin A, Cogswell IE, Crosby SW, Cunningham B, Harle AC, Maddison ER, Moitra M, Sahu M. Health sector spending and spending on HIV/AIDS, tuberculosis, and malaria, and development assistance for health: progress towards Sustainable Development Goal 3. The Lancet. 2020 Sep 5;396(10252):693-724
10. UNAIDS. Global AIDS Update ⁠— Seizing the moment ⁠— Tackling entrenched inequalities to end epidemics, Geneva. 2020. [cited 2021, Oct 23] Available from: <https://www.unaids.org/en/resources/documents/2020/global-aids-report>
11. UNAIDS. World Health Day Report 2020: Prevailing against pandemics by putting people at the centre. Geneva. 2020. [cited 2021, Oct 23]. Available from: <https://www.unaids.org/en/resources/documents/2020/prevailing-against-pandemics>
12. Global Fund. Description of the 2020-22 Allocation Methodology. 2019. [cited 2021, Oct 23]. Available at: <https://www.theglobalfund.org/media/9224/fundingmodel_2020-2022allocations_methodology_en.pdf?u=637122775470000000>
13. PEPFAR. PEPFAR 2020 Country Operational Plan Guidance for All PEPFAR Countries. Washington D.C. https://www.state.gov/wp-content/uploads/2020/01/COP20-Guidance.pdf2020.
14. PEPFAR. Strategy for Accelerating HIV/AIDS Epidemic Control (2017-2020). Washington D.C. 2017. [cited 2021, Oct 23]. Available at: <https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Strategy-for-Accelerating-HIVAIDS-Epidemic-Control-2017-2020.pdf>
15. UNAIDS. 2016. *Fast-Track Commitments to End AIDS by 2030*. Geneva.
16. UNAIDS. 2021. End Inequality. End AIDS. Global AIDS Strategy 2021-2026. Geneva.
17. Stover, J, Glaubius, R, Teng, Y, Kelly, S, Brown, T, Hallett, TB, Revill, P, Bärnighausen, T, Phillips, AN, Fontaine, C, Frescura, L, Izazola-Licea, JA, Semini, I, Godfrey-Faussett, P, De Lay, PR, Benzaken, AS & Ghys, PD 2021, 'Modeling the epidemiological impact of the UNAIDS 2025 targets to end AIDS as a public health threat by 2030', *Plos medicine*, vol. 18, no. 10, pp. e1003831
18. Egger M, Johnson L, Althaus C, Schöni A, Salanti G, Low N, Norris SL. Developing WHO guidelines: time to formally include evidence from mathematical modelling studies. F1000Research. 2017;6.
19. Revill P, Glassman A. Understanding the Opportunity Cost, Seizing the Opportunity: Report of the Working Group on Incorporating Economics and Modelling in Global Health Goals and Guidelines | Center For Global Development. 2019. [cited 2020, Jun 1] Available from: <https://www.cgdev.org/publication/understanding-opportunity-cost-seizing-opportunity-report-working-group>
20. OECD. Paris Declaration and Accra Agenda for Action - OECD. In Paris: OECD Publishing. 2005. [cited 2021, Oct 23]. Available at: https://doi.org/10.1787/9789264098084-en
21. Bojke L, Soares M, Claxton K, Colson A, Fox A, Jackson C, Jankovic D, Morton A, Sharples L, Taylor A. Developing a reference protocol for structured expert elicitation in health-care decision-making: a mixed-methods study. Health Technology Assessment (Winchester, England). 2021 Jun;25(37):1.
22. Woods B, Schmitt L, Rothery C, Phillips A, Hallett TB, Revill P, Claxton K. Practical metrics for establishing the health benefits of research to support research prioritisation. BMJ global health. 2020 Aug 1;5(8):e002152.
23. United Nations. 75/284 Political Declaration on HIV and AIDS: Ending Inequalities and Getting on Track to End AIDS by 2030. In Agenda Item No. 10, New York: 75th United Nations General Assembly. 2021. [cited 2021, Nov 5]. Available at: <https://undocs.org/A/RES/75/284>
24. Erondu NA, Aniebo I, Kyobutungi C, Midega J, Okiro E, Okumu F. Open letter to international funders of science and development in Africa. Nature Medicine. 2021 May;27(5):742-4.
25. Delva W, Wilson DP, Abu-Raddad L, Gorgens M, Wilson D, Hallett TB, Welte A. HIV treatment as prevention: principles of good HIV epidemiology modelling for public health decision-making in all modes of prevention and evaluation. PLoS Medicine. 2012 Jul 10;9(7):e1001239.
26. World Health Organization. UHC Compendium: Interventions for Universal Health Coverage. 2021. [cited2021, Oct 23]. Available at: <https://www.who.int/universal-health-coverage/compendium>
27. Kasprowicz VO, Chopera D, Waddilove KD, Brockman MA, Gilmour J, Hunter E, Kilembe W, Karita E, Gaseitsiwe S, Sanders EJ, Ndung’u T. African-led health research and capacity building-is it working?. BMC public health. 2020 Dec;20(1):1-0.